AF / 1642

# IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

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| Applicant(s): Agus et al. | |
| Application No.: 09/674,975 | |
| Filed: 11/07/2000 | Group Art Unit: 1642 |
| Title: Composition and Methods for Active Vaccination | Examiner: S. Ungar |
| Attorney Docket No.: MSK.P-039 | |

## BRIEF FOR APPELLANT

This brief is filed in support of Applicants' Appeal from the final rejection mailed 1/21/2004. Consideration of the application and reversal of the rejections are respectfully urged.

### Real Party in Interest

The real party in interest is Sloan-Kettering Institute for Cancer Research.

### Related Appeals and Interferences

To Applicants' knowledge, there are no related appeals or interferences.

### Status of Claims

Claims 9-13, 16, 17 and 21-24 are pending in this application and are the subject of this appeal. Claims 1-8, 14, 15, and 18-20 have been canceled. No other claims have been presented. Claim 11 is considered only in part by the Examiner as a result of an election of Seq. ID No. 1.

Status of Amendments

All amendments have been entered.

Summary of Invention

The present invention relates to a method for active vaccination against B cells expressing CD20. CD20 is a transmembrane protein that is expressed by both normal and malignant B cells during parts of the B cell development cycle. (Specification, Page 1). "Active vaccination" means that a material is administered which brings about the induction of an antibody immune response to CD20. (Specification, Page 2). A substantial difficulty arises in accomplishing this result, however, because CD20 is a self protein that is normally present. As such, the protein is "tolerated" or not recognized by the immune system as foreign, and merely adminitering CD20 or a portion thereof is not effective. The method of the invention overcomes this difficulty by administering to a patient a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, or a xenogeneic homolog thereof, coupled to a carrier protein effective to break tolerance to the transmembrane protein and a pharmaceutically acceptable adjuvant. The invention also provides a vaccine composition useful in this method comprising at least an immunogenic portion of the extracellular domain of the transmembrane protein, or a xenogeneic homolog thereof, coupled to a carrier protein effective to break tolerance to the transmembrane protein and a pharmaceutically acceptable adjuvant, wherein the transmembrane protein is CD20.

Issues on Appeal

1. Are claims 9, 10, and 11 (in part, as directed to Seq. ID No. 1), 12, 13, 16-17 and 21-24 enabled and therefore in compliance with 35 USC § 112, first paragraph?

2. Do claims 9, 10, and 11 (in part, as directed to Seq. ID No. 1), 12, 13, 16-17 and 21-24 define a patentable invention which is not obvious (35 USC § 103) over the cited art?

Applicants submit that both of these questions should be answered in the affirmative.

Grouping of Claims

As to the first rejection, claims 9-13, 16-17 and 21-24 are argued as a group and stand or fall together.

As to the second rejection,

Argument

Claims 9-13, 16, 17 and 21-24 are enabled.

Claims 9-13, 16-17 and 21-24 stand rejected under 35 USC § 112, second paragraph, as lacking enablement. The Examiner acknowledges that enablement exists for a partial CD20 sequence as defined in Seq. ID No. 1, or for the full length CD20 sequence. (Office Action of 7/29/2003, Page 9) The Examiner argues that this is not sufficient to enable the full scope of the claims, because "one cannot extrapolate the teaching of the specification to the scope of the claims because it is well known in the art that it is unpredictable that production of antibodies to linear fragments of amino acids will in fact produce antibodies that will bind to the wild-type amino acid sequence as it is exposed on the cell surface." (Office Action of 7/29/2003, Page 11). The Examiner's argument is thus that one cannot generally predict which portions of a linear sequence will be immunologically effective, and that the examples provided in this case are therefore insufficient. Applicants respectfully disagree with this contention for several reasons.

First, the Examiner has mischaracterized both the extent of variability in this case, and the extent of the examples provided. The claims require the use of "at least an immunogenic portion of the extracellular domain of CD20." The extracellular domain of CD20 is only 79 amino amino acids in length, and it's sequence has been fully provided for two species, both mouse and human. From each of these extracellular domain, a 44 amino acid fragment has been identified

and tested and shown to be effective for purposes of the invention. Thus, the specification provides clear guidance in the selection of this region of the two full length extracellular domains. Furthermore, Table 1 in the specification provides additional sequences from CD20. This teaching, taken together can be summarized diagrammatically by aligning the various fragments from the human sequence as follows:

*** = 44 amino acid fragment

+++ = first entry in Table 1

XXX = second entry in Table 1

QQQ = third entry in Table 1

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Val Lys Gly Lys Met Ile Met Asn Ser Leu Ser Leu Phe Ala Ala Ile


Ser Gly Met Ile Leu Ser Ile Met Asp Ile Leu Asn Ile Lys Ile Ser
                                                    *** *** ***

His Phe Leu Lys His Glu Ser Leu Asn Phe Ile Arg Ala His Thr Pro
*** *** *** *** *** *** *** *** *** *** *** *** *** *** *** ***
                                +++ +++ +++ +++ +++ +++ +++ +++
                                    XXX XXX XXX XXX XXX XXX XXX
    QQQ QQQ QQQ QQQ QQQ QQQ QQQ QQQ QQQ QQQ

Tyr Ile Asn Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser Glu Lys Asn
*** *** *** *** *** *** *** *** *** *** *** *** *** *** *** ***
+++ +++
XXX XXX

Ser Pro Ser Thr Gln Tyr Cys Tyr Ser Ile Gln Ser Leu Phe Leu
*** *** *** *** *** *** *** *** ***
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The Examiner has not explained why, given this teaching, the person skilled in the art would need undue experimentation to practice the claimed invention.

Furthermore, although the Examiner chooses to say it is really the same sequence because it spans the same range of amino acids, Applicants have also disclosed a further sequence, which

is the mouse counterpart of the 44 amino acid sequence. These sequences are not in fact the same, as reflected in the following residue by residue comparison in which the differences in the sequence are shown.

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Hu- Lys Ile Ser His Phe Leu Lys Met Glu Ser Leu Asn Phe Ile Arg Ala
Mu- Thr Leu --- --- --- --- --- --- Arg Arg --- Glu Leu --- Gln Thr

His Thr Pro Tyr Ile Asn Ile Tyr Asn Cys Glu Pro Ala Asn Pro Ser
Ser Lys --- --- Val Asp --- --- Asp --- --- --- Ser --- Ser ---

Glu Lys Asn Ser Pro Ser Thr Gln Tyr Cys Tyr Ser
--- --- --- --- --- --- --- --- --- --- Asn ---
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Thus, the Examiner's refusal to consider them as separate examples of the invention is inappropriate.

The examples in the application direct the person skilled in the art to two alternative 44 amino acid molecules and to segments within one of these that are useful in the invention. The Examiner characterizes this as insufficient based on generalized statements about unpredictability and unsubstantiated speculation about structural forms that might occur, and an assertion of requiring random testing. This is not sufficient in this case, because Applicants provide specific and focused guidance as to the location of the fragments to be used, and there is no reason provided to anticipate that if a 44 amino acid fragment and a shorter overlapping fragment are both effective that fragments of intermediate length would not be generally effective as well, particularly where a sequentially-different linear fragment is also shown to work.

It is also interesting to note that part of the Examiner's evidence of unpredictability in this case is the effectiveness of sequences when coupled with the carrier protein that were shown to be ineffective in the prior art. The Examiner states that "it appears that the findings in the application are unexpected and therefore, the broadly claimed invention is not enabled." (Office Action of 1/21/2004, Page 5). Leaving aside for the moment the question of how this position is consistent with the obviousness rejection discussed below, Applicants submit that this evidence actually works against the Examiner's position on enablement. The Examiner has admitted that

even sequences that are not useful in the absence of the carrier protein have been shown to be useful in the present invention. Thus, it is reasonable to conclude that requirements for utility in this invention are less stringent than was discussed in the art cited by the Examiner. As such, the generalized assertions of unpredictability have not been shown to be applicable.

For these reasons, Applicants submit that the rejection of claims 9-13, 16-17 and 21-24 as lacking enablement should be reversed.

The Claims Are Patentable Over the Art

Claims 9-13, 16-17 and 21-24 stand rejected under 35 USC § 103 as obvious over Mahoney et al. in view of Kwak et al and US Patent No. 5,830,731. In making a rejection under 35 USC § 103, it must be remembered that "obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 140, 231 USPQ 644, 647 (Fed. Cir. 1986) (citing *ACS Hosp. Syss., Inc. v. Montefiore Hosp.*, 732 F.2d 1572, 1577, 221 USPQ 929, 933 (Fed. Cir. 1984)). "[T]he factual inquiry whether to combine references must be thorough and searching." *McGinley v. Franklin Sports, Inc.*, 262 F.3d 1339, 1351-52, 60 USPQ2d 1001, 1008 (Fed. Cir. 2001). This factual question cannot "be resolved on subjective belief and unknown authority," *In re Lee*, 277 F.3d 1338, 1343-44, 61 USPQ2d 1430, 1434 (Fed. Cir. 2002); "it must be based on objective evidence of record." Id. at 1343, 61 USPQ2d at 1434.

In the present case, the Examiner has cited Maloney for a teaching that CD20 is a suitable target for the treatment of B cell lymphoma. Maloney, however, presents a problem, because the passive immunization methodology employed requires creation of patient-specific antibodies. Quite evidently, Maloney recognized the need for better treatment regimen that would not require patient-specific therapeutics, but did not see an obvious alternative to meet this need.

Kwak describes the use of a patient-specific anti-idiotype vaccine directed against a surface immunoglobulin found on B cells. The vaccine contains an idiotypic determinant conjugated with an immunogenic carrier protein such as KLH. This surface immunoglobulin in Kwak is not CD20, or related to CD20. Furthermore, Kwak suffers from the same problem as Mahoney, i.e., the vaccine's made were specific for each patient.

The '731 patent relates to cloning vectors and a cloning methodology for cell surface antigens. The patent provides a list of such antigens, that includes CD20. The patent also provides a generalized list of uses to which the various antigens can be put, which includes treatment of plasma neoplasms. There is no link in the '731 patent between any antigen, and any specific use to which that antigen may be put. Thus, the linkage that the Examiner is making, i.e, the selection of CD20 antigen, and the selection of plasma neoplasms, and the specific subset of B cell lymphoma, is based entirely on the present application and not on the specific teaching of reference.

Based on the teachings of Maloney and Kwak, and the selective reading of the '731 patent, the Examiner asserts that the present invention would have been obvious. This assertion is made even though the present invention provides a non-patient-specific vaccine, while both Maloney and Kwak are patient-specific compositions.

It may be reasonably presumed that if persons skilled in the art thought that simply using CD20 with a carrier protein and an adjuvant as now claimed would have been successful, they would have done so, rather than exploring the much more difficult and costly avenues reflected in Maloney and Kwak. Mahoney even specifically says such a therapy would be desirable, but does not recognize any method of attaining it. This is plain indication of a recognized and significant need in the art and thus evidence that the invention is not obvious. The Examiner chooses to ignore this evidence, however, calling it irrelevant in vie of the "clear teachings of the prior art references." These teachings, however, are nothing more than a collection of isolated information selected using hindsight knowledge of Applicants invention, and does not present a *prima facie* case of obviousness. The U.S. Court of Appeals for the Federal Circuit has stated that "[t]he mere fact that the prior art may be modified in the manner suggested by the Examiner does not make the modification obvious unless the prior art suggested the desirability of the

modification." *In re Fritch*, 972 F.2d 1260, 1266, 23 USPQ2d 1780, 1784 (Fed. Cir. 1992) (*citing In re Gordon,* 733 F.2d 900, 902, 221 USPQ 1125, 1127 (Fed. Cir. 1984)). Although this statement is couched in terms of modifying the prior art, it is equally applicable to combining teachings found in the prior art. Specifically, the mere fact that teachings found in the prior art could be combined as proposed by an examiner does not make the combination obvious "absent some teaching, suggestion or incentive supporting the combination." *Carella*, 804 F.2d at 140, 231 USPQ at 647 (citing ACS Hosp. Syss., Inc., 732 F.2d at 1577, 221 USPQ at 933). Stated differently, "citing references which merely indicate the isolated elements ... are known is not a sufficient basis for concluding that the combination of elements would have been obvious." *Ex Parte Hiyamizu*, 10 USPQ 2d 1393, 1394 (POBAI 1988).

In this regard, it should be noted that the references cited by the Examiner in support of the enablement rejection lend credence to the general unpredictability of the art, and to the inadequacy of some epitopes of CD20 to induce an immune response, presumably as a result of tolerance. It is completely incongruous therefore that the Examiner should assert that an anti-idiotype reaction, an immune response to an entirely different type of antigen, should give rise to an expectation that active immunization to any antigen at all (and to CD20 in particular) will give rise to an immune response. Further, there is no reasonable reading of the '731 patent which would allow selection of the combination of the specific antigen (CD20) and the specific use (treatment of neoplasms) without reliance on the present specification.

For these reasons, Applicants submit that the rejection under 35 USC § 103 is in error and should be reversed.

Respectfully submitted,

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## CLAIMS ON APPEAL

1-8 (canceled)

9. A method for active vaccination against B cells expressing CD20 comprising administering to a patient a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, or a xenogeneic homolog thereof, coupled to a carrier protein effective to break tolerance to the transmembrane protein and a pharmaceutically acceptable adjuvant.

10. The method claim 9, wherein the carrier protein is keyhole limpet hemocyanin.

11. The method of claim 9, wherein the vaccine composition comprises a peptide having the sequence given by Seq. ID No 1 or 2.

12. A method for treatment of B cell non-Hodgkin's lymphoma, comprising administering to a patient suffering from B cell non-Hodgkin's lymphoma a vaccine composition comprising at least an immunogenic portion of the extracellular domain of CD20, or a xenogeneic homolog thereof, coupled to a carrier protein effective to break tolerance to CD20 and a pharmaceutically acceptable adjuvant.

13. A vaccine composition comprising at least an immunogenic portion of the extracellular domain of the transmembrane protein, or a xenogeneic homolog thereof, coupled to a carrier protein effective to break tolerance to the transmembrane protein and a pharmaceutically acceptable adjuvant, wherein the transmembrane protein is CD20.

14-15 (canceled)

16. The composition of claim 13, wherein the vaccine composition comprises a peptide having the sequence given by Seq. ID No 1 or 2.

17. The composition of claim 13, wherein the carrier protein is keyhole limpet hemocyanin.

18 - 20. (canceled)

21. The method of claim 12, wherein the vaccine composition comprises a peptide having the sequence given by Seq. ID No. 1 or 2.

22. The method of claim 21, wherein the carrier protein is keyhole limpet hemocyanin.

23. The method of claim 12, wherein the carrier protein is keyhole limpet hemocyanin.

24. The method of claim 16, wherein the carrier protein is keyhole limpet hemocyanin.